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Original Investigation

State-Dependent Differences in Emotion Regulation Between Unmedicated Bipolar Disorder and Major Depressive Disorder

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IMPORTANCE Major depressive disorder (MDD) and bipolar disorder (BD) are difficult to distinguish clinically during the depressed or remitted states. Both mood disorders are characterized by emotion regulation disturbances; however, little is known about emotion regulation differences between MDD and BD. Better insight into these differences would be helpful for differentiation based on disorder-specific underlying pathophysiological mechanisms. Previous studies comparing these disorders often allowed medication use, limiting generalizability and validity. Moreover, patients with MDD and BD were mostly compared during the depressed, but not the remitted, state, while state might potentially modulate differences between MDD and BD.

OBJECTIVE To investigate positive and negative emotion regulation in medication-free patients with MDD and BD in 2 mood states: depressed or remitted.

DESIGN, SETTING, AND PARTICIPANTS A cross-sectional study conducted from May 2009 to August 2013 comparing behavioral and functional magnetic resonance imaging emotion regulation data of 42 patients with MDD, 35 with BD, and 36 healthy control (HC) participants free of psychotropic medication recruited from several psychiatric institutions across the Netherlands.

INTERVENTION A voluntary emotion regulation functional magnetic resonance imaging task using positive and negative pictures.

MAIN OUTCOMES AND MEASURES Behavioral and functional magnetic resonance imaging blood oxygen level–dependent responses during emotion regulation.

RESULTS In the remitted state, only patients with BD showed impaired emotion regulation ($t = 3.39$; $P < .001$; Cohen $d = 0.70$), irrespective of emotion type and associated with increased dorsolateral prefrontal cortex activity compared with those with MDD and healthy control participants ($P = .008$). In the depressed state, patients with MDD and BD differed with regard to happy vs sad emotion regulation ($t = 4.19$; $P < .001$; Cohen $d = 1.66$) associated with differences in rostral anterior cingulate activity ($P < .001$). Patients with MDD regulated sad and happy emotions poorly compared with those with BD and healthy control participants, while they demonstrated no rostral anterior cingulate difference between happy and sad emotion regulation. In contrast, patients with BD performed worse than those with MDD on sad emotion regulation but normal on happy emotion regulation, and they demonstrated significantly less rostral anterior cingulate activity while regulating happy compared with sad emotions.

CONCLUSIONS AND RELEVANCE Medication-free patients with MDD vs BD appear to differ in brain activations during emotion regulation, both while depressed and in remission. These different neuropathophysiological mechanisms between MDD and BD may be useful for further development of additional diagnostic tools.

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Distinguishing between major depressive disorder (MDD) and bipolar disorder (BD) is important because treatment strategies and prognosis differ.[1-3] Current diagnostic tools (questionnaires and clinical interviews) poorly differentiate between MDD and BD[4-6] during depression or remission, emphasizing the need for validated biomarkers to facilitate diagnostic procedures. Better insight into underlying neural mechanisms of both disorders may aid in the development of such biomarkers.

Major depressive disorder and BD share disturbances in emotion processing and regulation,[7-10] reflected by functional and structural frontolimbic alterations. *Emotion regulation* refers to cortical control over limbic regions. More automatic processes involve predominantly medial prefrontal cortical (PFC) structures, including the anterior cingulate cortex (ACC), orbitofrontal cortex, and dorsomedial PFC, as well as the (para)hippocampus. More voluntary processes additionally recruit lateral prefrontal cortical regions (dorsolateral PFC [DLPFC] and ventrolateral PFC [VLPFC]).[11] Patients with MDD show lateral PFC hyperfunction or hypofunction (during automatic or voluntary emotion regulation, respectively), while BD is associated with VLPFC and ventromedial PFC hypofunction. Furthermore, both disorders are characterized by predominantly decreased frontolimbic connectivity.[11-14]

Direct comparisons of emotion processing and regulation between MDD and BD are sparse[14] and the results are inconclusive. Regarding emotion processing, in depressed patients with BD (BDd) vs MDD (MDDd), both increased (eg, amygdala, thalamus, and hippocampus)[15,16] and decreased (eg, insula and temporal cortex)[17] activity in response to negative and/or positive emotional stimuli were reported. Moreover, Grotegerd et al[18] found increased amygdala activity in response to sad stimuli in MDDd but to happy stimuli in BDd, whereas Fournier et al[19] observed the reverse pattern.

Regarding emotion regulation, 2 studies found no differences in attentional control over positive or negative emotional pictures between MDDd and BDd,[20,21] whereas for neutral pictures, patients with MDDd demonstrated greater dorsal anterior cingulate activity than BDd.[21] For cognitive control over negative emotions, decreased VLPFC and dorsomedial PFC activity in MDDd vs BDd was reported.[22] One study comparing remitted MDD (MDDr) and BD (BDr) reported differential prefrontal activity patterns during attentional control over happy, but not sad, emotional stimuli.[23]

These conflicting findings may be explained, at least partly, as resulting from medication use in previous studies (except as in the study by Cerullo et al[20]). Antidepressants and mood stabilizers impact emotion regulation–related brain regions (eg, the amygdala and DLPFC).[24-35] Consequently, different medication classes used for MDD and BD may have had differential effects on neural activity. Moreover, to further delineate underlying neuropathophysiology, it is important to understand whether differences between MDD and BD are state or trait effects. However, studies comparing MDD and BD so far have been conducted in depressed patients only (except in the study by Matsubara et al[23]).

To expand our knowledge of emotion regulation in MDD and BD across mood states without medication confounds, we investigated emotion regulation differences between medication-free patients with MDD and with BD, either in depressed or remitted states, using a validated functional magnetic resonance imaging (fMRI) paradigm featuring reappraisal of emotional pictures. Because earlier studies suggested that negative and positive emotion regulation may differ between MDD and BD, we used positive and negative emotional pictures.[12,18,36-38] Present literature does not allow very specific hypotheses; however, given BD's vulnerability for recurrent (hypo)manic episodes, we hypothesized that particularly positive emotion regulation would differentiate between MDD and BD, being impaired only in BD, both during remission[23] and depression.[18]

Methods

Participants

Medication-free currently depressed and remitted patients with MDD and BD-I/BD-II were recruited from several psychiatric institutions across the Netherlands via general practitioners, advertisements, patient organizations, and other research projects. For inclusion and exclusion criteria, see the eAppendix in the Supplement.

This study, conducted from May 2009 to August 2013, was approved by the Academic Medical Center Medical Ethical Committee. Patients participated after providing written informed consent; they received €40 (US $43.41) and travel expenses.

Demographics and Clinical Characteristics

Six patients were excluded because of poor or incomplete data (eAppendix in the Supplement). Major depressive disorder (MDDr: n = 21; MDDd: n = 21) and BD (BDr: n = 26; BDd: n = 9) were comparable regarding age, sex, education, IQ, age at illness onset, illness duration, and comorbid anxiety (all $P > .05$). Hamilton Depression Rating Scale[39,40] scores differed between depressed and remitted patients ($P < .001$) but not between MDD and BD within the remitted/depressed groups ($P > .05$). The number of previous major depressive episodes was higher in BDd vs MDDd ($P = .02$) (**Table 1**). Healthy control (HC) individuals (n = 36) were comparable with patients regarding age, sex, education, and IQ ($P > .05$).

Emotion Regulation Paradigm

Similar to previous emotion regulation studies,[41-47] patients viewed pictures of different emotional categories (sad, happy, fearful, and neutral) (eTable 1 in the Supplement) and were instructed to passively experience (attend condition) or actively regulate through distancing (regulate condition) any emotion elicited (see eFigure 1, eTable 2, and the eAppendix in the Supplement for details). Distancing, rather than situation-focused reappraisal, was chosen as the regulation strategy[48] because distancing was easier to apply for depressed patients. Distancing involves the process of becoming a detached observer by thoughts such as: "This is only a

Table 1. Demographic and Clinical Characteristics[a]

Characteristic	Mean (SD)					All Groups		MDDr vs BDr		MDDd vs BDd	
	HC (n = 36)	MDDr (n = 21)	BDr [10 BD-II] (n = 26)	MDDd (n = 21)	BDd [6 BD-II] (n = 9)	F/χ^2	*P* Value	t/χ^2	*P* Value	t/χ^2	*P* Value
Age	40.2 (10.8)	42.0 (10.4)	42.7 (10.7)	44.0 (8.9)	40.1 (10.9)	0.56	.69	0.24	.81	0.94	.35
Sex											
Male	11	8	10	6	4	1.27	.87	0.01	.98	0.71	.40
Female	25	13	16	15	5						
Education[b]											
Low	1	2	2	3	0	12.33	.14	0.23	.89	1.74	.41
Middle	6	7	7	10	4						
High	29	12	16	8	5						
No. of previous MDEs, median (range)[c]	0	4.0 (2-20)	6.5 (2-20)[d]	3.0 (2-20)	10 (3-20)	...	**<.001**	...	.21[e]	...	**.006**[e]
IQ	105.0 (13.1)	101.7 (9.8)	101.5 (9.5)	96.8 (16.5)	102.0 (12.1)	1.41	.23	0.07	.95	0.95	.35
Age at illness onset, y	...	23.5 (9.4)	23.6 (8.7)	25.5 (8.4)	20.8 (8.4)	0.64	.59	0.02	.98	1.36	.18
Duration of illness, y	...	19.9 (10.8)	19.2 (10.5)	17.9 (10.1)	19.6 (12.7)	0.14	.94	0.23	.82	0.40	.69
HDRS score[f]	1.3 (1.7)	6.3 (5.2)	5.5 (5.5)	21.6 (5.4)	22.8 (7.1)	87.10	**<.001**	0.57	.57	0.62	.54
Comorbid anxiety disorder[g]	0	3	2	3	2	1.39	.71	0.53	.47	0.29	.59
Medication naive	...	5	2	6	1	7.18	.30	2.38	.22	1.68	.57
Duration of medication-free period, mo[h]											
1-3	...	4	6	4	2	7.0	.34	5.51	.09	0.31	>.99
>3-12	...	1	9	2	2						
>12	...	8	6	7	4						
Duration of remission[i]											
1 wk-3 mo	...	7	7	...	...	...	...	2.07	.39	...	...
>3-12 mo	...	4	10	...	...						
>12 mo	...	7	6	...	...						
History of substance use disorder	...	4	13	6	3	4.97	.18	4.37	.06	0.07	>.99
Duration of remissions of substance use disorder, mo[j]											
3-6	...	0	4[j]	0	1	4.52	.26	1.98	.28	2.25	.33
>6	...	4	7	6	2						
Current substance use[k]											
Alcohol	31	14	20	13	8	5.86	.21	0.60	.50	2.18	.21
Tobacco	7	5	9	7	4	3.97	.43	0.77	.52	0.34	.69
Drugs (incidental)	4	1	4	0	0	4.97	.30	1.26	.37	...	...
Benzodiazepine use, No.	...	0	1[l]	1[m]	1[n]	2.15	.84	0.83	>.99	0.41	>.99

Abbreviations: BDd, bipolar disorder depressed state; BDr, bipolar disorder remitted state; HDRS, Hamilton Depression Rating Scale; HC, healthy control; IQ, intelligence quotient; MDDd, major depressive disorder depressed state; MDEs, major depressive episodes; MDDr, major depressive disorder remitted state; ellipses, not applicable.

[a] Within the depressed and remitted groups, there were no significant differences between MDD and BD regarding demographic or clinical characteristics, except for the number of previous episodes. The boldface type indicates a significant result, corrected for multiple testing.

[b] Low: primary education or preparatory middle-level applied education; middle: higher general continued education or middle-level applied education; and high: preparatory scientific education, higher applied education, or scientific education.

[c] More than 20 episodes are set on 20 episodes.

[d] Three missing values.

[e] Kruskall-Wallis test comparing medians.

[f] 17-Item HDRS.

[g] Hypochondria, specific phobia, social phobia, panic disorder, and obsessive-compulsive disorder.

[h] Missing values: 3 for MDDr, 3 for BDr, and 2 for MDDd; all patients were at least 1 month free of medication.

[i] Missing values: 3 for MDDr and 3 for BDr.

[j] Missing values: 2 for BDr.

[k] Alcohol/cannabis abuse/dependence until 5 to 6 months before scanning.

[l] Lorazepam, 2.5 mg; quit 17 hours before scanning.

[m] Oxazepam, 25 mg; quit 48 hours before scanning.

[n] Temazepam, 20 mg; quit 40 hours before scanning.

picture," "This has nothing to do with me," and "This picture is fake." In contrast, situation-focused reappraisal requires more complicated cognitive processes: patients need to reframe the situation depicted in such a way that the meaning of the situation becomes more neutral (eg, when people are shown crying, one could think, "They are crying for joy, not sadness").[48]

After the scan, patients judged all pictures on valence, arousal, and emotional intensity of 5 basic emotions (sadness, fear, disgust, anger, and happiness) (eTable 3 and eTable 4 in the Supplement). This task was included to assess possible between-group differences in baseline emotional appraisal of pictures because these might influence regulation performance (analyses presented in the eAppendix in the Supplement).

MRI Scanning

Magnetic resonance imaging data were acquired on a 3.0-T MRI scanner (Philips Intera, Philips Medical Systems) with an 8-channel SENSE head coil (eAppendix in the Supplement).

Analyses

Behavioral Data

To assess differences in emotion regulation success between MDD and BD, we calculated in-scan regulation success scores for each emotion by expressing the difference between mean emotional intensities (attending minus regulating) as the percentage of the mean emotional intensity during attending. Neutral pictures were not regulated and therefore not used to assess between-group emotion regulation differences. Regulation success scores were arcsine transformed to meet normality assumptions.

To assess diagnosis and state and emotion effects, a regulation success score was entered as a dependent variable in a linear mixed model regression analysis (IBM SPSS Statistics version 20), with diagnosis (MDD/BD), state (depressed/remitted), and emotion (sad/fear/happy) as independent variables. The significance threshold was set at $P < .003$ (Bonferroni corrected for 16 post hoc tests). Significant main effects were followed up with post hoc tests. Because HC individuals were only euthymic and we primarily investigated MDD/BD differences, HC individuals were not included in this model. To assess whether those with MDD and/or BD differed from HC individuals, we compared either remitted or depressed patients with MDD and BD with HC individuals in separate mixed models. Further details regarding behavioral data are in the eAppendix in the Supplement.

Functional MRI Data

Statistical parametric mapping (SPM; http://www.fil.ion.ucl.ac.uk/spm/software/spm8/) was used for fMRI data analysis (eAppendix in the Supplement).

Main effects for task were assessed by calculating individual statistical maps for attend emotion greater than attend neutral and regulate emotion greater than attend emotion and feeding these into second-level 1-sample *t* tests.

For assessment of blood oxygen level–dependent activity differences between MDD and BD, contrasts of interest were based on behavioral results (see further on), indicating that MDDr and BDr differed regarding overall emotion regulation, irrespective of emotion type (regulate emotion > attend emotion), and MDDd and BDd differed regarding happy vs sad emotion regulation (regulate happy > attend happy)>(regulate sad > attend sad). These contrasts were entered into second-level random effects analyses using 1-way analyses of variance. We additionally report a 2 × 2 factorial design for each contrast to test for diagnosis-by-state interactions (eAppendix in the Supplement).

We studied 7 regions of interest (ROIs)[38,41,42,44,48]: the amygdala, thalamus, insula, DLPFC (Brodmann area 9/46), ACC, medial PFC (Brodmann area 8), and hippocampus. We report results surviving family-wise error, small-volume correction for bilateral anatomical ROIs (WFU Pickatlas version 2.4[49,50]) or surviving whole-brain family-wise error correction. We applied Bonferroni correction to account for the number of ROIs, adjusted for the mean correlation ($r = 0.18$) between ROIs, rendering an equivalent corrected α of .01 (http://www.quantitativeskills.com/sisa/calculations/bonfer.htm). The effects of task performance on task-related blood oxygen level–dependent activity were assessed with correlation analyses (eAppendix in the Supplement).

Results

Behavioral Data

There was a significant diagnosis-by-state-by-emotion interaction ($F = 5.25$; $P = .006$) (**Figure 1**; eTable 5 in the Supplement).

In the remitted group, there were no diagnosis-by-emotion interactions (all $P \geq .80$; Figure 1A). Therefore, we compared regulation success scores between MDDr and BDr across emotions. Patients with BDr were significantly less successful in emotion regulation than those with MDDr ($t = 3.39$; $P < .001$; Cohen $d = 0.70$). Only BDr differed significantly from HC individuals ($t = 4.64$; $P < .001$; $d = 0.94$).

In the depressed group (Figure 1B), there was a significant effect of diagnosis on the difference in regulation success scores between happy vs sad emotions ($t = 3.86$; $P < .001$): patients with BDd, but not MDDd, showed significantly stronger regulation of happy compared with sad emotions ($t = 4.19$; $P < .001$; $d = 1.66$). There were no significant effects of diagnosis on the differences in regulation success scores for fear (all $P \geq .02$).

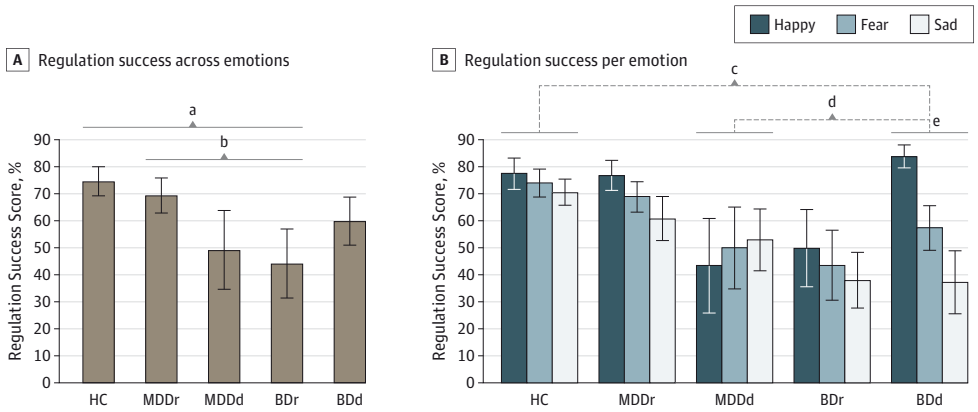
Patients with MDDd were less successful regulating happy emotions than HC individuals ($t = 3.045$; $P = .003$; $d = 0.85$), whereas those with BDd were trendwise less successful regulating sad emotions than HC individuals ($t = 2.77$; $P = .006$; $d = 0.6$), with a trendwise diagnosis (HC individuals vs BDd)-by-emotion (happy vs sad) interaction ($t = 2.92$; $P = .004$).

Functional MRI Data

Main Task Effects

Both attend emotion greater than attend neutral and regulate emotion greater than attend emotion were associated with expected regional brain activity (ie, limbic regions for attend emotion > attend neutral and regulatory regions [supplementary motor area and medial frontal cortex] for regulate > attend) (eFigure 2 and eTable 6 in the Supplement).

Figure 1. Emotion Regulation Success Scores in the Different Patient Groups



There was a significant diagnosis-by-state-by-emotion interaction (F = 5.25; P = .006) explained by the following pattern: A, Across all emotions, remitted patients with bipolar disorder (BDr) (n = 26) performed significantly worse on emotion regulation compared with both remitted patients with major depressive disorder (MDDr) (n = 21; footnote b) and healthy control (HC) individuals (n = 36; footnote a). There were no differences between depressed patients with MDD (MDDd) and BD (BDd) on overall emotion regulation. B, When emotions were separated, there was a significant diagnosis-by-(happy vs sad) emotion regulation interaction in the depressed group (footnote d): depressed patients with BD (n = 9) regulated happy emotions better than sad emotions (footnote e), whereas depressed patients with MDD (n = 21) and HC individuals (n = 36) showed no difference between happy and sad emotion regulation success scores. Furthermore, there was a trendwise significant diagnosis (HC vs BDd)-by-emotion (happy vs sad) interaction (footnote c). There were no significant emotion-specific differences between remitted patients with MDD and BD. The solid lines above the bars indicate a difference between 2 means and the dashed lines indicate an interaction effect. Error bars represent 95% CIs.

[a] t = 4.64; P < .001; significant difference.

[b] t = 3.39; P < .001; significant difference.

[c] t = 2.92; P = .004, trendwise significant interaction.

[d] t = 3.86; P < .001; significant interaction.

[e] t = 4.19; P < .001; significant difference.

Table 2. Activity Differences for Regulate Greater Than Attend Between MDD and BD[a]

Comparison	Area	Side	Cluster Size	Peak Voxel (MNI), mm			t
				x	y	z	
Across Emotions, MDDr vs BDr							
MDDr>BDr	None	...	...	...	...	...	...
BDr>MDDr	Inferior frontal gyrus, pars triangularis/ opercularis (BA 46)[b]	Right	27	40	16	34	4.63
Happy>Sad, MDDd vs BDd							
MDDd>BDd	Rostral anterior cingulate cortex (BA 32)	Right	61	10	36	6	5.05
BDd>MDDd	None	...	...	...	...	...	...

Abbreviations: BA, Brodmann area; BD, bipolar disorder; BDd, bipolar disorder depressed state; BDr, bipolar disorder remitted state; MDD, major depressive disorder; MDDd, major depressive disorder depressed state; MDDr, major depressive disorder remitted state; MNI, Montreal Neurological Institute; ellipses, not applicable.

[a] Results are significant at P < .009, family-wise error corrected for the bilateral anatomical regions on interest.

[b] Also significant at P < .05, family-wise error corrected across the whole brain (k = 2; t = 5.41).

Remitted State and Regulation Across Emotions

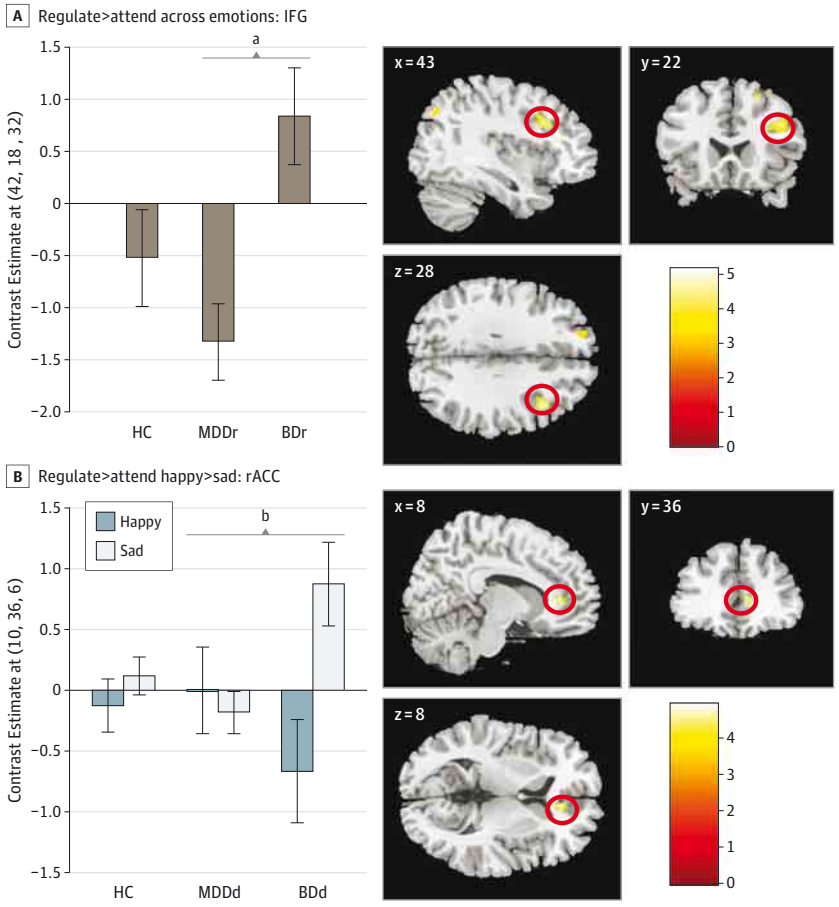
Behavioral data showed that MDDr and BDr, but not MDDd and BDd, differed regarding overall emotion regulation (**Table 2**; **Figure 2**A). Testing this in the fMRI data using planned comparisons showed a significant difference in DLPFC (inferior frontal gyrus and inferior frontal gyrus) activity between MDDr and BDr for regulate emotion greater than attend emotion (greater in BDr), collapsed over all emotions (P = .008). This effect was not observed in MDDd and BDd, corresponding to the behavioral results. The 2 × 2 factorial design additionally revealed a diagnosis-by-state interaction in the inferior frontal gyrus (uncorrected P < .001; eTable 7 in the Supplement); this interaction did not survive multiple comparison correction (eAppendix in the Supplement).

There were no differences in DLPFC activity between those with MDDr or BDr and HC individuals.

Depressed State and Regulation of Sad vs Happy Emotions

Behavioral data indicated that MDDd and BDd, but not MDDr and BDr, differed regarding happy vs sad emotion regulation. Comparing (regulate happy > attend happy)>(regulate sad > attend sad) in MDDd vs BDd revealed a significant difference in rostral ACC (rACC) activity (P < .001) (Table 2; Figure 2B). In BDd, we found a decrease in rACC activity during regulation of happy emotions and an increase during regulation of sad emotions, which were absent in MDDd. In accordance with behavioral results, this effect was not observed in MDDr and BDr. The 2 × 2 factorial design furthermore revealed a diagnosis-

Figure 2. Regional Activity Differences Associated With Differences in Emotion Regulation Success Within the Remitted (A) and Depressed (B) Subgroups



A, Across emotions, remitted patients with bipolar disorder (BDr) demonstrated significant greater dorsolateral prefrontal cortex activity than remitted major depressive disorder (MDDr) (footnote a). Compared with healthy control (HC) individuals, differences were not significant. B, In contrast to depressed patients with MDD (MDDd), those with BP (BDd) demonstrated a decrease in rostral anterior cingulate cortex (rACC) activity during regulation of happy emotions and an increase in rACC activity during regulation of sad emotions (footnote b). Compared with HC individuals, only those with BDd differed (trendwise) significantly (k = 43; t = 4.42; P = .015, small-volume corrected for a bilateral ACC region of interest). IFG indicates inferior frontal gyrus.

[a] k = 31; t = 4.83; P = .006, Small-volume corrected for bilateral Brodmann area 9/46 region of interest.

[b] k = 48; t = 4.79; P = .004, Small-volume corrected for a bilateral ACC region of interest.

by-state interaction in the rACC (uncorrected P < .001; eTable 7 in the Supplement); this interaction did not survive multiple comparison correction (eAppendix in the Supplement).

Compared with HC individuals, patients with BDd demonstrated nonsignificantly lower rACC activity for (regulate happy > attend happy)>(regulate sad > attend sad) (P = .049).

Adjustment for Previous Episodes

Results did not change after adjusting for the number of previous major depressive episodes (eTable 8 in the Supplement).

Correlation Analysis

There were no correlations between regulation success scores and DLPFC or rACC activity.

Discussion

This fMRI study indicates that medication-free patients with MDD and BD differ regarding emotion regulation, and that these differences are mood state dependent. During remission, BDr but not MDDr, showed impaired emotion regulation across emotions. During depression, MDDd and BDd differed regarding happy vs sad emotion regulation: BDd showed impaired sad, but unexpectedly normal happy, emotion regulation, whereas in MDDd, both sad and happy emotion regulation were compromised. These emotion regulation difficulties were associated with DLPFC and rACC activity. Both regions have been implicated in the specific regulation strategy we applied (distancing).[11,51-53] The DLPFC is thought to be involved in effortful modulation of limbic regions, operating indirectly by feedback via the orbitofrontal cortex.[11] The rACC may operate via a feedforward mechanism and is involved in the evaluation of emotional and motivational information, automatic redirection of attention away from emotional stimuli, emotional conflict resolution, and emotional expression.[11,53-55] We discuss the findings for remitted and depressed patients separately.

Remitted MDD vs BD

Whereas task performance was similar in those with MDDr and HC individuals, those with BDr performed worse on overall emotion regulation, which was associated with greater DLPFC activity. This suggests that increased DLPFC activity reflects increased, but still insufficient, regulation attempts in BDr, which may also explain the lack of significant correlations between DLPFC activity and regulation success.

Our finding contrasts with decreased DLPFC and VLPFC activity in BDr reported previously,[42] perhaps owing to different reappraisal strategies (situation focused vs self-focused), which have been associated with different prefrontal cortical regions.[48] Nevertheless, increased DLPFC activity in BDr has also been demonstrated with other emotion regulation tasks.[56-58]

In MDDr, emotion regulation was apparently normal, in line with previous behavioral studies.[59] However, Kanske et al[59] demonstrated altered orbitofrontal cortex and amygdala activity suggestive of sustained emotion regulation abnormalities in MDDr, albeit with situation-focused reappraisal. We suggest that distancing may have been easier to apply for our patients with MDDr than the more complicated situation-focused reappraisal, suggesting that emotion regulation by distancing may differentiate MDDr from BDr.

Depressed MDD vs BD

Both MDDd and BDd differed regarding happy vs sad emotion regulation. However, the performance of those with MDD and BD was discordant with our expectation: those with BDd showed normal performance on happy, but not on sad, emotion regulation, whereas those with MDDd performed equally poorly on both sad and happy emotion regulation.

Importantly, postscan ratings of emotional intensity of sad and happy pictures (eAppendix in the Supplement) revealed that patients with MDDd perceived sad pictures less negative and happy pictures less positive than those with BDd (ie, ratings for negative/positive valence were less extreme in those with MDDd than in those with BDd) (eTable 3 in the Supplement). Also, experiencing happiness in response to happy pictures was mixed with sadness in MDDd (eTable 4 in the Supplement). Therefore, patients with MDDd may not have been fully capable of experiencing positive emotions in response to happy pictures, in agreement with the emotional context insensitivity hypothesis in MDD (ie, blunted general emotional experience).[60] In contrast, such blunting was not present in our BDd sample, in line with previous findings in BD of extremely negative, but also extremely positive, appraisals of internal states,[61] increased rumination in response to negative and positive affect,[62] and increased limbic activity in response to both negative and positive emotional faces.[16]

The difference in appraisal of positive emotions may partly explain the discrepancy in behavioral regulation success between MDDd and BDd. Speculatively, we propose that in BDd, happy pictures evoked happy and thus mood incongruent emotions, for which distancing is probably easy, whereas in MDDd, happy pictures also evoked mood congruent (ie, sad) emotions, for which distancing is more difficult. Indeed, in MDDd, sad intensity of happy pictures correlated (trendwise significantly) negatively with regulation success ($\tau = -0.28$; $P = .07$; eFigure 3 in the Supplement), indicating more difficult regulation for sad emotions elicited by these happy pictures.

The difference in appraisal of positive emotions may also partly explain the disparity in rACC activity between MDDd and BDd, which may reflect differences in emotional conflict experience.[63] Regulation of mood congruent emotions (decreasing emotions in accordance with mood state) may create an emotional conflict and hence activate the rACC, whereas regulation of mood incongruent emotions (decreasing emotions discordant with mood state) may deactivate the rACC. Therefore, in BDd, regulation of positive emotions elicited by happy pictures may have resolved emotional conflict, deactivating the rACC (Figure 2B), whereas regulation of negative emotions (sad pictures) created emotional conflicts, activating the rACC. In those with MDDd, emotions were less intense; hence, emotional conflict experience may have been subdued, leaving rACC reactivity virtually absent (eFigure 4 in the Supplement).

Possible Implications for Differences in Treatment Response and Prognosis

Dysfunctional DLPFC-rACC interaction is thought to interfere with normal reduction of rACC and amygdala activity during cognitive or emotional challenges and thus with adequate cognitive control of emotion, leading to maladaptive rumination and eventually treatment resistance.[55] Our results of increased DLPFC activity and increased rACC reactivity in BD vs MDD may indicate qualitatively different frontocingulate dysregulation in BD, which, tentatively, may explain why BD generally responds less well to antidepressants[64] or cognitive behavioral therapy.[65] Furthermore, whereas patients with MDDr resembled HC individuals, those with BDr demonstrated behavioral emotion regulation impairments despite DLPFC hyperactivity, suggesting residual neuropsychological and neural deficits, which may increase relapse vulnerability. Moreover, compensatory frontal activity displayed by patients with BDr may deplete cognitive resources, leading to cognitive impairments,[55,66] which consequently may negatively impact daily functioning, recovery, and antidepressant treatment.[67-71] Thus, our findings of increased DLPFC activity in BDr, but not in MDDr, and qualitative differences in frontocingulate dysfunction correspond to the observation that patients with BD usually have a worse prognosis than those with MDD.

Limitations and Strengths

Some limitations should be considered. First, the BDd sample size was small, limiting statistical power. However, we still found behavioral and neural activity differences between those with BDd vs with MDDd and HC individuals, indicating robust effects. Second, we included only recurrent MDD, so results cannot be extrapolated to single-episode MDD. However, given the recurrent nature of BD, this choice likely enhances overall validity of the study. Third, owing to our cross-sectional design we could not establish whether MDD/BD differences result from a preexisting vulnerability to specifically develop either mood disorder or from scarring due to previous (hypo)manic episodes in BD. Fourth, our MDD and BD samples may not fully represent the MDD and BD population because patients were able to manage without medication, at least for a certain period. However, comparing these possibly less severe MDD/BD samples may, if anything, have reduced the likelihood of detecting MDD vs BD differences. Fifth, a trendwise ($P = .06$) greater proportion of patients with BD than with MDD had a history of substance (predomi-

nantly alcohol) use disorder. Because in most cases the substance use disorder concerned abuse rather than dependence and was in remission for more than a year, a substantial impact on our results appears unlikely.

The strengths of our study were the inclusion of medication-free patients, excluding the possibility that MDD/BD differences were mediated by different medication classes. Second, by inclusion of depressed and remitted patients, we demonstrated state-by-diagnosis interactions, revealing state-specific differences between BD and MDD. Third, by selecting only those with MDD with a negative BD family history and an illness duration of 5 years or more, we reduced the risk of including patients with latent BD in the MDD group.

Conclusions

This study demonstrated that medication-free remitted patients with MDD and BD differ regarding overall emotion regulation associated with differences in DLPFC activity, whereas medication-free depressed patients with MDD and BD differ regarding happy vs sad emotion regulation associated with differences in emotional appraisal and rACC activity. These results corroborate previous findings indicating that during depression, MDD and BD may differ particularly regarding happy vs sad emotion processing/regulation. Furthermore, emotion regulation impairments in BD, but not MDD, appear to be still present during remission. These state-specific emotion regulation differences may represent different underlying pathophysiological mechanisms, which may be useful for individual classification of patients with MDD and BD. Eventually, such investigations may be incorporated in a hierarchical diagnostic pipeline for mood disorders, combining clinical characteristics (such as *DSM-5* criteria) with additional neuropsychological investigations and, for example, imaging biomarkers to resolve remaining diagnostic uncertainty. Future studies should assess this possibility in medication-naive patients with different levels of depression severity.

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